REMARKS

The Specification has been amended to include a cross reference to the applications to which the instant application claims priority.

Claim 9 has been canceled.

Claims 1-3 and 5 have been amended to require that R has at least two carbon atoms. Support for the amendment can be found in the Specification on page 6, lines 8-12.

Claim 5 has also been amended as an independent claim, incorporating formula (I) from claim 1.

New claims 10-12 have been introduced. Support for these claims is drawn from original claim 5 and claims 2-4.

New claim 13 has been introduced. Support for this claim can be found in the Specification on page 21, line 16 to page 22, line 13.

No new matter has been added.

Objections to the Specification

The Examiner has objected to the Specification for failing to provide a cross reference to the applications to which the instant application claims priority.

Applicants have amended the Specification to provide such cross reference, thereby obviating the objection.

Objections to the Claims

The Examiner has objected to claim 5 as being dependent upon a rejected base claim, stating that the claim would be allowable if written in independent form to include all of the limitations of the base claim and any intervening claims.

Applicants have redrafted claim 5 as an independent claim incorporating all of the limitations of claim 1, thereby obviating the objection.

The Examiner has objected to claim 9 as a substantial duplicate of claim 8.

Applicants have canceled claim 9, thereby obviating the objection.

Rejections Under 35 USC § 112, first paragraph

The Examiner has rejected claim 9 as lacking enablement. The Examiner's extensive comments are presented on pages 2-7 and are not reproduced here.

Applicants that claim 9 has been canceled, thus the rejection is moot.

Rejections Under 35 USC § 102

The Examiner has rejected claims 1-3, 8 and 9 as anticipated by Hayashi and Narasaka and Kuramochi et al. The Examiner states that Hayashi and Narasaka disclose the compound epolactaene on page 313 while Kuramochi et al. disclose the same compound on page 7373. The Examiner states that epolactaene is equivalent to Applicants' claimed compound of formula (I) where R is Me.

Applicants have amended the claims to exclude R as Me, thereby overcoming the rejection.

Rejections Under 35 USC § 103

The Examiner has rejected claims 1-4, 8 and 9 as obvious over Hayashi and Narasaka. The Examiner states that Hayashi and Narasaka teach a compound of formula (I) where R is Me. The Examiner contends that adjacent homologues and structural isomers are generally so similar that substitution of a variable with such constituents would be obvious. She contends that the motivation to make the claimed compounds derives from the expectation that structurally similar compounds are generally expected to have similar properties and have similar utilities. Thus, the skilled artisan would have been motivated to use such homologues with the expectation that the resulting products would all have similar activity. Applicants respectfully traverse.

The composition disclosed in Hayashi and Narasaka, namely Epolactaene, contains a Me group in the R position and is excluded from the scope of claims 1-3. In addition, the claimed invention provides an excellent neuroblastoma growth-inhibitory activity compared to Epolactaene. As can be seen from the accompanying Declaration of Dr. Kakeya, a side-by-side comparison of Epolactaene and a compound of claimed formula (I) where R is t-Bu indicates that the claimed invention provides superior results. Here, the compound of the invention had a 50% growth-inhibiting concentration of 0.4 μg/ml as compared to Epolactaene's 2.0 μg/ml. That is, the compound of the invention had 5 times more efficacy than did Epolactaene. This is important because administering a lower drug dosage to a patient to obtain the same effect drastically reduces any potential side-effects. Furthermore, neither Hayahi and Narasaka nor Kuramochi et al. disclose nor suggest that the Epolactaene analogs would show an excellent neuroblastoma growth-inhibitory effect at all.

In view of the above, Applicants respectfully request reconsideration and removal of the rejection.

All of the claims remaining in the case, including those newly entered claims, are submitted to be novel, nonobvious, patentable subject matter and Applicants urge favorable action and early allowance of the claims.

If the Examiner has any questions concerning this application, the Examiner is strongly urged to contact Susan Gorman (Reg. No: 47,604) at the telephone number of the undersigned below to schedule an Interview.

Pursuant to the provisions of 27 C.F.R. §§ 1.17 and 1.136(a), Applicants petition for an extension of two (2) months time for the period in which to file a response to the outstanding Office Action. The Commissioner is hereby authorized to charge Deposit Account 02-2448 the sum of $450 in connection with the filing of this amendment.

If necessary, the Commissioner is hereby authorized in this, concurrent and future replies, to charge payment or credit any overpayment to our Deposit Account 02-2448 for any additional fees required under 37.C.F.R. § 1.16 or under § 1.17, particularly extension of time fees.

Dated: April 24, 2007

Respectfully submitted,

#47,604

By _____

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PATENT

IN THE U.S. PATENT AND TRADEMARK OFFICE

Applicant:	Hiroyuki OSADA et al.	Conf.:	6909
Appl. No.:	10/516,743	Group:	1626
Filed:	May 26, 2005	Examiner:	Karen, Cheng
For:	NOVEL COMPOUND HAVING ANTITUMOR ACTIVITY AND PROCESS FOR PRODUCING THE SAME		

DECLARATION SUBMITTED UNDER 37 C.F.R. § 1.132

Honorable Commissioner
Of Patents and Trademarks
P.O. Box 1450
Alexandria, VA 22313-1450

Mar 31, 2007

Sir:

I, Dr. Hideaki Kakeya of the Antibiotics Lab., Discovery Research Institute, Riken, Japan, do hereby declare the following:

I have attached a copy of my curriculum vitae to this Declaration.

I am a vice-chief scientist, Antibiotics Lab., Discovery Research Institute, RIKEN and have worked in this field for 13 years.

I am familiar with the above referenced patent application and the area of science dealing with identification of novel compounds for use as antitumor drug candidates and drugs. I am also well versed in the use of antitumor agents for treatment of cancer.

I have read and understand the subject matter of the Office Action of November 24, 2006.

The following comments are offered in support of the patentability of the instant invention.

The Examiner states that the invention of this application (i.e. 10/516,743; "'743") is obvious. The Examiner refers to the Hayashi and Narasaka reference (chemistry Letters (1998) pages 313-314) and states that because the Hayashi and Naraska composition has a methyl group in the R position, adjacent homologues of CO_2R (for example ethyl, proply, etc.) would be expected to work the same without evidence to the contrary.

As a preliminary measure, the claims in the '743 application has been changed to require at least two carbons for the substituents for the R group.

In order to provide the unexpected results required by the Examiner, I conducted the following experiment.

To compare the action of the Epolactaene drug of Hayashi and Narasaka and the compound of the '743 application where R is t-BU in general formula I, a series of dilutions was made for each compound. An aliquot from each dilution was added to human neuroblastoma SH-SY5Y cells that were cultured in DMEM medium containing 5% fetal bovine serum. The cells were then cultured at 37°C under a 5% carbon dioxide atmosphere for 48 hours. A MTT (3-(4,5-dimethly-thiazol-2-yl)-2,5-diphenyl tetrazolium bromide) reagent was then added and the cells further cultured for another 2 to 4 hours. To calculate the survival ratio, absorbance at 570 nm was measured in each case and the 50% growth-inhibition concentration was determined.

The results indicated that Epolactaene has a 50% growth-inhibition concentration of 2.0 μg/ml. On the other hand, the compound of the '743 application where R is t-BU

In general formula I has a 50% growth-inhibition concentration of 0.4 μg/ml. In other words, the compound of the '743 application was 5 times more efficacious in inhibiting the growth of the neuroblastoma cells than was Hayashi and Narasaka' Epolactaene. This is important because administering a lower drug dosage to a patient to obtain the same effect drastically reduces any potential side-effects. Thus, the compound of the '743 application is superior to Epolactaene as an antitumor agent.

To conclude, in my opinion the current application is not obvious over the Epolactaene compound disclosed in the Hayashi and Narasaka reference.

The undersigned hereby declares that all statements made herein based upon knowledge are true, and that all statements made based upon information and belief are believed to be true; and further, that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code, and that such willful false statements may jeopardize the validity of the application or any patent issued thereon.

DATED: Mar. 31, 2007

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Update: Feb. 1, 2007

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@ Publication List (For Hideaki KAKEYA)

@ 75 original papers & @ 24 reviews

@ original paper :

75) Y. Asami, H. Kakeya, G. Okada, M. Toi, H. Osada. RK-95113, a new angiogenesis inhibitor produced by Aspergillus fumigatus. J. Antibiot. 59, 724-728, 2006.

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RKTS-33, an epoxycyclohexenone derivative that specificically inhibits Fas ligand-dependent apoptosis in CTL-mediated cytotoxicity. Biosci. Bitechnol. Biochem. 69, 1923-1928, 2005.

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retinoblastoma protein by phosmidosine, a nucleotide antibiotic. Cancer Res., 58, 704-710, 1998.

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cell cycle inhibitors, tryprostatins A, B and other diketopiperazines produced by *Aspergillus fumigatus*. I. Taxonomy, fermentation, isolation and biological properties. J. Antibiot., 49, 527~533, 1996.

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